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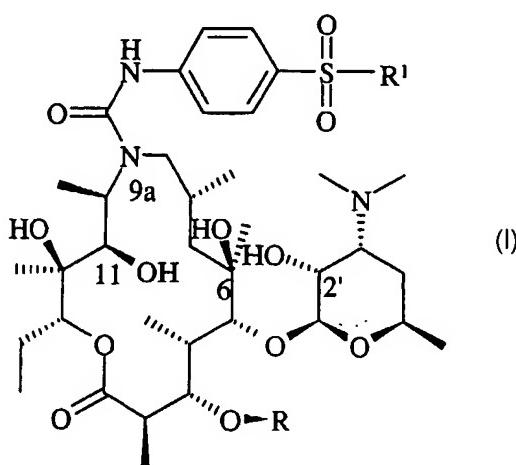
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(54) Title: SUBSTITUTED 9A-N-{N'-[4-(SULFONYL)PHENYL]CARBAMOYL} DERIVATIVES OF 9-DEOXO-9-DI-HYDRO-9A-AZA-9A-HOMOERITHROMYCIN A AND 5-O-DESOSAMINYL-9-DEOXO-9-DI-HYDRO-9A-AZA-9A-HOMOERITHRONOLIDE A



(57) Abstract: The invention relates to substituted 9a-N-{N'-[4-(sulfonyl)phenyl]carbamoyl} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-di-hydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series general formula (1), wherein R represents H or cladinosyl moiety and R1 represents chloro, amino, phenylamino, 2-pyridylamino, 3,4-dimethyl-4-isoxazolylamino and 5-methyl-3-isoxazolylamino group, and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, to the process for their preparation of pharmaceutical composition as well as the use their compositions for sterilization rooms and medical instruments as well as for protection of wall and wooden coatings.

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Substituted 9a-N-[N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A

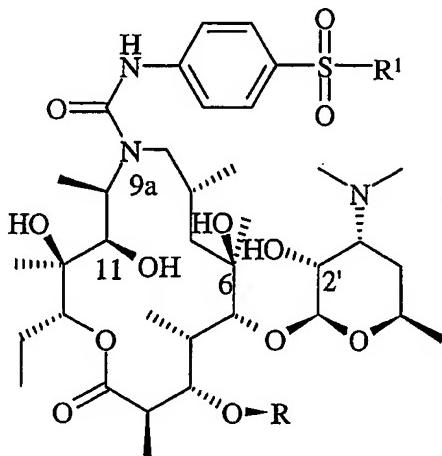
5 **Technical Field**

Int. Cl. C07H17/08, A61K31/71

Technical problem

10 The present invention relates to substituted 9a-N-[N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series having antibacterial activity of the general formula 1

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1

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wherein R represents H or cladinosyl moiety, and R¹ represents chloro, amino, phenylamino, 2-pyridylamino, 3,4-dimethyl-5-isoxazolylamino and 5-methyl-3-isoxasolylamino group, to pharmaceutically acceptable addition salts thereof with

25 inorganic or organic acids, to a process for the preparation of the pharmaceutical compositions as well as to the use of pharmaceutical compositions obtained in the treatment of bacterial infections.

Prior Art

30 Erythromycin A is a macrolide antibiotic , whose structure is characterized by 14-membered macrolactone ring having carbonyl group in C-9 position. It was found by McGuire in 1952 [*Antibiot. Chemother.*, 2 (1952) 281] and for over 50 years it has been considered as a reliable and effective antimicrobial agent in the treatment of diseases caused by Gram-positive and some Gram-negative microorganisms. However, in an acidic medium it is easily converted into anhydroerythromycin A, an inactiv C-6/C-12 metabolite of a spiroketal structure [P. Kurath et al., *Experientia* 27 (1971) 362].It is well-known that spirocyclisation of aglycone ring of erythromycin A is successfully inhibited by a chemical transformation of C-9 ketones or hydroxy groups in C-6 and/or C-12 position. By the oximation of C-9 ketones [S. Đokić et al., *Tetrahedron Lett.* 1967: 1945] and by subsequently modifying the obtained 9(E)-oxime into 9-[O-(2-methoxyethoxy)methyloxime] erythromycin A (ROXITHROMYCIN) [G. S. Ambrieres, Fr. Pat. 2,473,525, 1981] or 9(S)-erithromycylamine [R. S. Egan et al., *J. Org. Chem.* 39 (1974) 2492] or a more complex oxazine derivative thereof, 9-deoxo-11-deoxy-9,11-{imino[2-(2-methoxyethoxyethylidene]-oxy}-9(S)-erythromycin A (DIRITHROMYCIN) [P. Lugar i sur., *J. Crist. Mol. Struct.* 9 (1979) 329], novel semisynthetic macrolides were synthetised, whose basic characteristic, in addition to a greater stability in an acidic medium, is a better pharmacokinetics and a long half-time with regard to the parent antibiotic erythromycin A. In a third way for modifying C-9 ketones use is made of Beckmann rearrangement of 9(E)-oxime and of a reduction of the obtained imino ether (G. Kobrehel i sur., U.S. Pat. 4,328,334, 1982.) into 11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo-9a-aza-9a-homoerythromycin A) under broadening the 14-member ketolactone ring into a 15-member azalactone ring. By reductive N-methylation of 9a-amino group according to Eschweiler-Clark process (G. Kobrehel et al., BE Pat. 892,397, 1982.) or by a preliminary protection of amino group 45 by means of conversion into the corresponding N-oxides and then by alkylation and 50 55

reduction [G. M. Bright et al., U.S. Pat., 4,474,768, 1984.] N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxy-9a-methyl-9a-aza-9a-homoerithromycin A, AZITHROMYCIN) was synthetized, a prototype of azalide antibiotics, which, in addition to a broad antimicrobial spectrum including Gram-negative bacteria and intracellular microorganisms, are characterized by a specific mechanism of transport to the application site, a long biological half-time and a short therapy period. In EP A 0316128 (G. M. Bright et al.) novel 9a-allyl and 9a-propargyl derivatives of 9-deoxy-9a-aza-9a-homoerythromycin A are disclosed and in U.S. Pat. 4,492,688, 1/1985 (Bright G. M.) the synthesis and the antibacterial activity of the corresponding cyclic ethers are disclosed. In the J. Antibiotics 46 (1993) 1239 (G. Kobrehel et al.) there are further disclosed the synthesis and the activity spectrum of novel 9-deoxy-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-cyclic carbamates and O-methyl derivatives thereof.

According to the known and established Prior Art, 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, a process for the preparation thereof as well as the preparation methods and use a pharmaceutical preparations have not been disclosed as yet.

It has been found and it is object of the present invention that substituted 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A, novel semisynthetic macrolide antibiotics of the azalide series and pharmaceutically acceptable addition salts thereof with inorganic or organic acids may be prepared by reacting ammonia or substituted amine with 9a-N-[N'-[4-sulfonylphenyl]carbamoyl] derivatives of 9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A which are obtained by reacting of -9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A with 4-(chlorosulfonyl)phenylisocyanate and optionally by reacting the obtained 9a-N-{N'-[4-(sulfonyl)phenyl]carbamoyl}

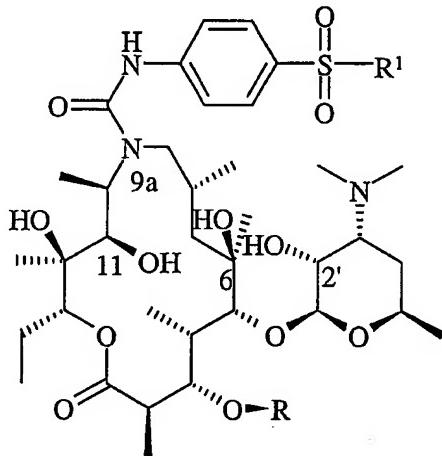
derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A with inorganic and organic acids.

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Technical Solution

It has been found that novel substituted 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula 1, wherein R represents H or cladinosyl group and R¹ represents chloro group,

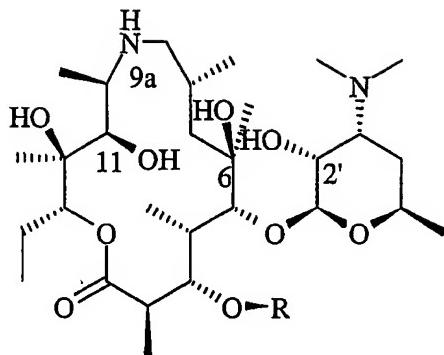
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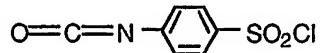
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may be prepared by reacting 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula 2,



2

wherein R represents H or cladinosyl group, with 4-(chlorosulfonyl)phenylisocyanate
110 formula 3,



3

after that the compounds of general formula 1 were obtained, in which R has previous
115 meaning, and R¹ represents Cl, by reaction of the compounds general formula 1 respectively, wherein R represents H or cladinosyl group and R¹ represents Cl, with ammonia or substituted amines general formula 4, wherein R² represents H, phenyl group, 2-pyridyl group, 3,4-dimethyl-5-isoxazolyl group or 5-methyl-3-isoxazolyl group,

120 $\text{R}^2\text{-NH}_2$

4

in toluene, xylene or some other aprotic solvent, at a temperature of 0°C to 110°C.
Pharmaceutically acceptable acid addition salts which also represents an object of the
125 present invention, were obtained by reaction of substituted 9a-N-[N'-(4-sulfonylphenylcarbamoyl)] derivatives of 9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A with an at least equimolar amount of the corresponding inorganic or organic acid such as hydrochloric acid, hydroiodic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, propionic acid, benzoic acid, benzene sulfonic acid, metane sulfonic

130 acid, lauryl sulfonic acid, stearic acid, palmitic acid, succinic acid, ethylsuccinic acid, lactobionic acid, oxalic acid, salicylic acid and similar acids, in a solvent inert to the reaction. Addition salts are isolated by evaporating the solvent or, alternatively, by filtration after a spontaneous precipitation or a precipitation by the addition of a non-polar cosolvent.

135 Substituted 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula 1 and pharmaceutically acceptable addition salts with inorganic or organic acids thereof possess an antibacterial activity *in vitro*.

140 Minimal inhibitory concentration (MIC) is defined as the concentration which shows 90% growth inhibition, and was determined by broth dilution methods according to National Committee for Clinical Laboratory Standards (NCCLS, M7-A2) protocols. Final concentration of test substances were in range from 64 to 0.125 µg/ml. MIC levels 145 for all compound were determined on panel of susceptible and resistant Gram positive bacterial strains (*S. aureus*, *S. pneumoniae* and *S. pyogenes*) and on Gram negative strains (*E. coli*, *H. influenzae*, *E. faecalis*, *M. catarrhalis*).

Test substances from Example 3 to 7 were active on susceptible strains of *S. pyogenes* (MIC 2 to 8 µg/ml), and on susceptible strains on *S. pneumoniae* (MIC 0.5 to 8 µg/ml). 150 Substances from Example 3 and 4 showed strong antimicrobial activities on *S. pyogenes* iMLS resistant strain (MIC 2 µg/ml).

155 The obtained results for substances from Example 3 to 7 expressed as MIC in mg/ml suggest a potential use thereof as sterilization agents of e.g. rooms and medical instruments and as industrial microbial agents e. g. for the protection of wall and wooden coatings.

Process for the preparation of 9a-N-{N'-[4-(sulfonyl)phenyl]carbamoyl} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desozaminy1-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A of this invention is illustrated by the following 160 Examples which should in no way be construed as a limitation of the scope thereof.

Example 1

165 9-Deoxo-9-dihydro-9a-N-{{[4-(chlorosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithromycin A}

A mixture of 1.35 g (1.84 mmol) 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 0.40 (1.84 mmol) 4-(chlorosulfonyl)phenylisocyanate and 30 ml dry toluene was stirred 1 hour at the temperature 0°-5°C. The reaction mixture was evaporated at 170 reduced pressure to dryness to give crude 9-deoxo-9-dihydro-9a-N-{{[4-(chlorosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithromycin A. The pure product was obtained, where from by chromatography the crude product on a silica gel column using solvent methylene chloride.

MS(ES⁺) m/z = 794.

175

Example 2

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-{{[4-(chlorosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithronolide A

Analogously to the process disclosed in Example 1, from 1.95 g (2.0 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A and 0.43 g (2.0 mmol) 4-(chlorosulfonyl)phenylisocyanate in 30 ml dry toluene crude product was obtained, wherefrom by chromatography on silica gel column using methylene chloride as a solvent. Pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-{{[4-(chlorosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithronolide A was obtained.

185

MS (ES+)m/z = 794.

Example 3

190 9-Deoxo-9-dihydro-9a-N-{{[4-(aminosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithromycin A

The solution of 1.35 g (1.84 mmol) 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 0.4 g (1.84 mmol) 4-(chlorosulfonyl)phenyl isocyanate in 30 ml dry toluene was

stirred about 1.0 hour at the temperature 0°- 5°C. In the reaction mixture 5.0 ml (4.55 g; 195 61.5 mmol) 23 % water solution of ammonia was added and the reaction mixture was stirred about 30 minutes at room temperature. The crude product was filtered, wherefrom by column chromatography on silica gel using solvent system methylen-chloride : methanol = 9 : 1. Pure 9-deoxo-9-dihydro-9a-N-{[4-(aminosulfonyl)phenyl]-carbamoyl}-9a-aza-9a-homoerithromycin A was obtained.

200

IR (KBr)/cm⁻¹ = 1727, 1638, 1593, 1552, 1126, 1013.

1H NMR (500 MHz; CDCl₃/δ) = 4.41 (1H, H-1'), 4.76 (1H, H-1''), 4.00 (1H, H-3), 3.41 (1H, H-5), 3.20 (3H, 3''-OCH₃), 2.89 (1H, 4''), 2.50 (6H, 3'-N'(CH₃)₂), 2.26 (1H, H-2'a), 1.51 (1H, H-2'b), 1.29 (1H, H-8), 0.96 (3H, 10-CH₃), 0.89 (3H 4-CH₃), 205 0.80 (3H, H-15).

¹³C NMR (500 MHz; CDCl₃/δ) = 175.6 (C-1), 155.5 (9a-NCONH), 101.9 (C-1'), 95.2 (C-1''), 84.1 (C-5), 78.3 (C-3), 48.8 (3''-OCH₃), 44.5 (C-2), 27.6 (C-8), 19.9 (8-CH₃), 9.2 (10-CH₃), 11.1 (C-15).

210

MS (ES⁺) m/z (%) = 933.

Example 4

9-Deoxo-9-dihydro-9a-N-[N'-[4-(phenylaminosulfonyl)phenyl]carbamoyl]-9a-aza-9a-homoerithromycin A

Analogously to the process disclosed in Example 3, from 1,35 g (1,84 mmol) 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A, and 0,4 g (1,84 mmol) 4-(chlorosulfonyl)phenyl isocyanate, 1,0 ml (11,0 mmol) aniline in 30 ml dry toluene 0,8 220 g pure 9-deoxo-9-dihydro-9a-N-[N'-[4-(aminosulfonyl)phenyl]carbamoyl]-9a-aza-9a-homoerithromycin A was obtained with following spectral data.

IR (KBr)/cm⁻¹ = 1727, 1638, 1593, 1552, 1126, 1013.

225 ^1H NMR (500 MHz; CDCl_3/δ) = 4.45 (1H, H-1'), 4.76 (1H, H-1''), 4.01 (1H, H-3),
3.38 (1H, H-5), 3.22 (3H, 3''-OCH₃), 2.90 (1H, 4''), 2.50 (6H, 3'-N'(CH₃)₂), 2.26
(1H, H-2'a), 1.52 (1H, H-2'b), 1.27 (1H, H-8), 0.90 (3H, 10-CH₃), 0.89 (3H 4-CH₃),
0.79 (3H, H-15).

230 ^{13}C NMR (500 MHz; CDCl_3/δ) = 179.0 (C-1), 155 (9a-NCONH), 103.8 (C-1'), 95.8
(C-1''), 84.7(C-5), 79.0 (C-3), 50.0 (3''-OCH₃), 46.5 (C-2), 27.9 (C-8), 20.4 (8-CH₃),
9.2 (10-CH₃), 11.3 (C-15).

MS (ES⁺) m/z (%) = 1009.

235

Example 5

9-Deoxo-9-dihydro-9a-N-[N'-[4-(2-pyridylaminosulfonyl)phenyl]carbamoyl]-9a-aza-
9a-homoerithromycin A

240 Analogously to the process disclosed in Example 3, from 1.35 g (1.84 mmol) 9-deoxo-
-9-dihydro-9a-aza-9a-homoerithromycin A, 0.4 g (1.84 mmol) 4-(chlorosulfonyl)phenyl
isocyanate and 0.70 g (5.2 mmol) 2-aminopyridine in 30 ml dry toluene 0.5 g pure 9-
-deoxo-9-dihydro-9a-N-[N'-[4-(2-pyridylaminosulfonyl)phenyl]carbamoyl]-9a-aza-9a-
-homoerithromycin A was obtained with following spectral data.

245

IR (KBr)/cm⁻¹ = 1727, 1638, 1593, 1552, 1126, 1013.

250 ^1H NMR (500 MHz; CDCl_3/δ) = 4.41 (1H, H-1'), 4.75 (1H, H-1''), 4.00 (1H, H-3),
3.38 (1H, H-5), 3.21 (3H, 3''-OCH₃), 2.89 (1H, 4''), 2.50 (6H, 3'-N'(CH₃)₂), 2.27
(1H, H-2'a), 1.48 (1H, H-2'b), 1.27 (1H, H-8), 0.89 (3H, 10-CH₃), 0.88 (3H 4-CH₃),
0.79 (3H, H-15).

255 ^{13}C NMR (500 MHz; CDCl_3/δ) = 175.6 (C-1), 155.4 (9a-NCONH), 101.9 (C-1'),
95.1 (C-1''), 84.0 (C-5), 78.1 (C-3), 48.8 (3''-OCH₃), 46.5 (C-2), 27.6 (C-8), 19.9 (8-
CH₃), 9.1 (10-CH₃), 11.1 (C-15).

MS (ES⁺) m/z (%) = 1014.

260

Example 6

9-Deoxo-9-dihydro-9a-N-[N'-[4-(3,4-dimethyl-5-isoxazolylaminosulfonyl)phenyl]-carbamoyl]-9a-aza-9a-homoerithromycin A

265

Analogously to the process disclosed in Example 3, from 1.35 g (1.84 mmol) 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A, 0.4 g (1.84 mmol) 4-(chlorosulfonyl)phenyl isocyanate and 0.41 g (3.67 mmol) 5-amino-3,4-dimethylisoxazole in 30 ml dry toluene 1.5 g pure 9-deoxo-9-dihydro-9a-N-[N'-[4-(3,4-dimethyl-5-isoxazolylaminosulfonyl)-phenyl]carbamoyl]-9a-aza-9a-homoerithromycin A was obtained.

270

MS (ES⁺) m/z (%) =1028.

Example 7

9-Deoxo-9-dihydro-9a-N-[N'-[4-(5-methyl-3-isoxazolylaminosulfonyl)phenyl]-carbamoyl]-9a-aza-9a-homoerithromycin A

275

Analogously to the process disclosed in Example 3, from 1.35 g (1.84 mmol) 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A, 0.4 g (1.84 mmol) 4-(chlorosulfonyl)phenyl isocyanate and 0.36 g (3.67 mmol) 3-amino-5-methylisoxazole in 30 ml dry toluene 0.40 g pure 9-deoxo-9-dihydro-9a-N-[N'-[4-(5-methyl-3-isoxazolylaminosulfonyl)-phenyl]carbamoyl]-9a-aza-9a-homoerithromycin A was obtained with following spectral data.

285

¹H NMR (500 MHz; CDCl₃/δ) = 4.42 (1H, H-1'), 4.75 (1H, H-1''), 4.01 (1H, H-3), 3.39 (1H, H-5), 3.20 (3H, 3''-OCH₃), 2.89 (1H, 4''), 2.50 (6H, 3'-N'(CH₃)₂), 2.24 (1H, H-2'a), 1.48 (1H, H-2'b), 1.28 (1H, H-8), 0.90 (3H, 10-CH₃), 0.87 (3H 4-CH₃), 0.79 (3H, H-15).

290 ^{13}C NMR (500 MHz; CDCl_3/δ) = 175.8 (C-1), 155.6 (9a-NCONH), 101.7 (C-1'), 95.8 (C-1''), 84.0 (C-5), 78.3 (C-3), 48.9 (3''-OCH₃), 45 (C-2), 27.8 (C-8), 20.2 (8-CH₃), 9 (10-CH₃), 11.3 (C-15).

MS (ES⁺) m/z (%) = 1014.

295 **Example 8**

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[4-(aminosulfonylphenyl)carbamoyl]-9a-aza-9a-homoerithronolide A

300 Analogously to the process disclosed in Example 3, from 1.15 g (2.0 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, 0.43 g (2.0 mmol) 4-(chlorosulfonyl)phenyl isocyanate and 5.0 ml (4.55 g; 61.5 mmol) 23 % water solution of ammonia in 30 ml xylene 0.60 g pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[4-(aminosulfonylphenyl)carbamoyl]-9a-aza-9a-homoerithronolide A was obtained with following spectral data.

305

^1H NMR (500 MHz; piridin/ δ) = 8.16, 7.93, 7.93, 7.5 (1H, fenilni), 5.60 (1H, H-13) 5.1 (1H, H-1'), 4.41 (1H, H-5) 4.30 (1H, H-3), 3.61 (1H, H-5''), 3.49 (1H, H-2''), 3.02 (1H, H-2), 2.61 (1H, H-3''), 2.21 (6H, 3'-N(CH₃)₂), 2.36 (1H, H-14a), 1.70 (1H, H-4'a), 1.87 (1H, H-14b), 1.69 (1H, H-4) 1.52 (1H, H-4'b), 1.58 (3H, 2-CH₃), 1.01 (3H, H-15).

310

^{13}C NMR (500 MHz; piridin/ δ) = 178 (C-1), 156.7 (NHCONH), 144.8, (fenil.), 133.2 (fenil.), 131.5, 129.3, 127.6, 115.3, (CH, fenil.), 103.3 (C-1''), 75.0 (C-13) 75.4 (C-3), 69.9 (C-5''), 69.2 (C-2'') 68.0 (C-5), 65.4 (C-3'') 45.6 (C-2), 40.3 (3'-N(CH₃)₂), 39.1 (C-4), 23.2 (C-14), 29.2 (C-4''), 16.7 (2-CH₃), 11.4 (C-15).

MS (ES⁺) m/z (%) = 775.

320

Example 95-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-[4-(phenylaminosulfonyl)phenyl]-carbamoyl]-9a-aza-9a-homoerithronolide A

325 Analogously to the process disclosed in Example 3, from 1.15 g (2.0 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, 0.43 g (2.0 mmol) 4-(chlorosulfonyl)phenyl isocyanate and 0.4 ml (0.419 g, 4.4 mmol) aniline in 30 ml dry toluene 0.70 g pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-[4-(phenylaminosulfonyl)phenyl]carbamoyl]-9a-aza-9a-homoerithronolide A was obtained with
330 following spectral data.

¹H NMR (500 MHz; CDCl₃/δ) = 4.35 (1H, H-1'), 3.86 (1H, H-3), 3.57 (1H, H-5'),
3.31 (1H, H-2'), 2.67 (1H, H-2), 2.5 (1H, H-3'), 2.30
(6H, 3'-N(CH₃)₂), 1.96 (1H, H-14a), 1.70 (1H, H-4'a),
1.56 (1H, H-14b), 1.30 (1H, H-4'b), 0.93 (3H, H-15).

¹³C NMR (500 MHz; CDCl₃/δ) = 175.8 (C-1), 105.3 (C-1'), 75.4 (C-3), 69.8 (C-5'),
68.9 (C-2') 64.6 (C-3') 44.7 (C-2), 39.6 (3'-N(CH₃)₂),
20.9 (C-14), 29.8 (C-4'), 10.4 (C-15).

340 MS (ES⁺) m/z (%) = 851.

Example 105-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-[4-(2-pyridylaminosulfonyl)phenyl]-carbamoyl]-9a-aza-9a-homoerithronolide A

345 Analogously to the process disclosed in Example 3, from 1.15 g (2.0 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, 0.43 g (2.0 mmol) 4-(chlorosulfonyl)phenyl isocyanate and 0.4 g (4.2 mmol) 2-aminopyridine in 30 ml dry toluene 0.80 g pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-[4-(2-pyridylaminosulfonyl)phenyl]carbamoyl]-9a-aza-9a-homoerithronolide A was obtained with
350 following spectral data.

355

¹H NMR (500 MHz; CDCl₃/δ) = 8.30, 7.64, 7.38, 7.64 (1H, aminopiridin), 4.34 (1H, H-1'), 3.84 (1H, H-3), 3.58 (1H, H-5'), 3.31 (1H, H-2'), 2.63 (1H, H-2), 2.6 (1H, H-3'), 2.29 (6H, 3'-N(CH₃)₂), 1.94 (1H, H-14a), 1.71 (1H, H-4'a), 1.55 (1H, H-14b), 1.29 (1H, H-4'b), 0.92 (3H, H-15).

360

¹³C NMR (500 MHz; CDCl₃/δ) = 141.5, 140.8, 114.5, 114.1 (aminopiridin), 105.4 (C-1'), 75.3 (C-3), 69.9 (C-5'), 68.9 (C-2') 64.6 (C-3') 44.7 (C-2), 39.6 (3'-N(CH₃)₂), 20.9 (C-14), 29.9 (C-4'), 10.4 (C-15).

MS (ES⁺) m/z (%) = 852.

Example 11

365

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-[4-(3,4-dimethyl-3-isoxazolylaminosulfonyl)phenyl]carbamoyl]-9a-aza-9a-homoerithronolide A

370

Analogously to the process disclosed in Example 3, from 1.15 g (2.0 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, 0.43 g (2.0 mmol) 4-(chlorosulfonyl)phenyl isocyanate and 0.45 g (4.0 mmol) 5-amino-3,4-dimethylisoxazole in 30 ml dry toluene 0.75 g pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-[4-(3,4-dimethyl-3-isoxazolylaminosulfonyl)phenyl]carbamoyl]-9a-aza-9a-homoerithronolide A was obtained with following spectral data.

375

MS (ES⁺) m/z (%) = 870.

Example 12

5-O-Desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-[4-(5-methyl-3-isoxazolylaminosulfonyl)phenyl]carbamoyl]-9a-aza-9a-homoerithronolide A

380

Analogously to the process disclosed in Example 3, from 1.15 g (2.0 mmol) 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A, 0.43 g (2.0 mmol) 4-(chlorosulfonyl)phenyl isocyanate and 0.39 g (4.0 mmol) 3-amino-5-methylisoxazole in 30 ml dry toluene 0.7 g pure 5-O-desosaminyl-9-deoxo-9-dihydro-9a-N-[N'-[4-(5-

385 -methyl-3-isoxazolylaminosulfonyl)phenyl]carbamoyl}-9a-aza-9a-homoerithronolide A
was obtained with following spectral data.

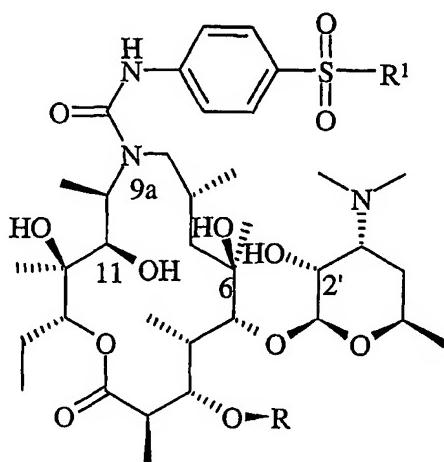
390 ^1H NMR (500 MHz; CDCl_3/δ) = 4.36 (1H, H-1'), 3.87 (1H, H-3), 3.56 (1H, H-5'),
3.32 (1H, H-2'), 2.65 (1H, H-2), 2.48 (1H, H-3'), 2.32
(6H, 3'-N(CH₃)₂), 1.95 (1H, H-14a), 1.70 (1H, H-4'a),
1.55 (1H, H-14b), 1.30 (1H, H-4'b), 0.90 (3H, H-15).

395 ^{13}C NMR (500 MHz; CDCl_3/δ) = 105.6 (C-1'), 74.6 (C-3), 69 (C-5'), 69.3 (C-2') 64.6
(C-3') 44 (C-2), 40.1 (3'-N(CH₃)₂), 21.4 (C-14), 30.2
(C-4'), 10.8 (C-15).

395 MS (ES⁺) m/z (%) = 856.

CLAIMS

- 400 1. Substituted 9a-N-{N'-[4-(sulfonyl)phenylcarbamoyl]} derivatives of 9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosamynil-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A of the general formula 1,

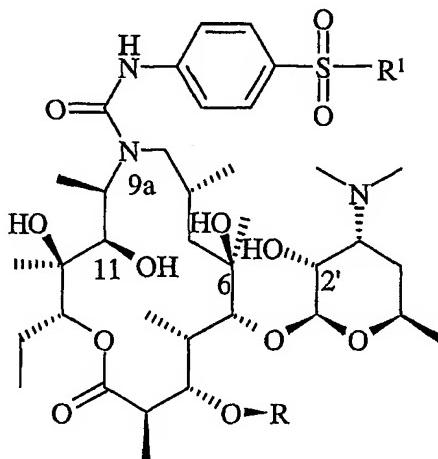


405

wherein R represents H or cladinosyl moiety, and R¹ represents chloro, amino, phenylamino, 2-pyridylamino, 3,4-dimethyl-5-isoxazolylamino and 5-methyl-3-isoxazolylamino group, and pharmaceutically acceptable addition salts thereof with inorganic or organic acids.

- 410 2. A substance according to claim 1, characterized in that R¹ represents chloro group and R represents cladinosyl moiety.
3. A substance according to claim 1 characterized in that R¹ represents chloro group, and R represents H.
4. Substance according to claim 1 where R¹ represents amino group, and R represents cladinosyl moiety.
- 415 5. A substance according to claim 1, characterized in that R¹ represents phenylamino group, and R represents cladinosyl group.
6. A substance according to claim 1, characterized in that R¹ represents 2-pyridylamino group, and R represents cladinosyl group.

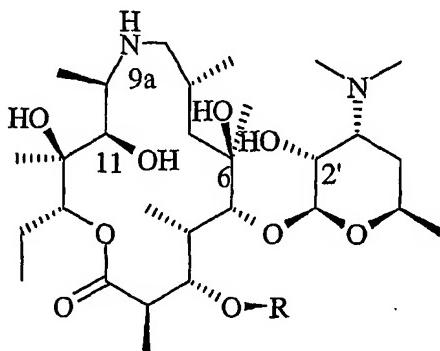
- 420 7. A substance according to claim 1, characterized in that R¹ represents 3,4-dimethyl-
-5-isoxazolyl group, and R represents cladinosyl moiety.
8. A substance according to claim 1, characterized in that R¹ represents 5-methyl-3-
-isoxazolylamino group, and R represents cladinosyl group.
9. A substance according to claim 1, characterized in that R¹ represents amino group
425 and R represents H.
10. A substance according to claim 1, characterized in that R¹ represents phenylamino
group, and R represents H.
11. A substance according to claim 1, characterized in that R¹ represents 2-
-pyridylamino group, and R represents H.
- 430 12. A substance according to claim 1, characterized in that R¹ represents 3,4-dimethyl-
-5-isoxazolylamino group, and R represents H.
13. A substance according to claim 1, characterized in that R¹ represents 5-methyl-3-
-isoxazolylamino group and R represents H.
14. A process for the preparation of substituted 9a-N-{N'-[4-(sulfonyl)phenyl
435 carbamoyl]} derivatives of 9-deoxy-9-dihydro-9a-aza-9a-homoerithromycin A and
5-O-desosaminyl-9-deoxy-9-dihydro-9a-aza-9a-homoerithronolide A of the general
formula 1,



1

- 440 wherein R¹ represents chloro, amino, phenylamino, 2-pyridylamino, 3,4-dimethyl-5-
-isoxazolylamino and 5-methyl-3-isoxazolylamino group and R represents H or
cladinosyl group, characterized in that 9a-N-{N'-[4-(chlorosulfonyl)phenyl]-

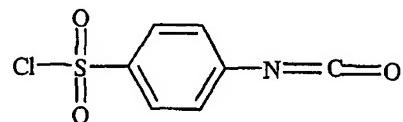
carbamoyl} derivatives of 9-deoxo-9-dihydro-9a-aza-9a-homoerithromycin A and 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A general formula 1, wherein R¹ represents chloro group and R represent H or cladinosyl group, which can be prepared by reaction of 9-deoxo-9-dihydro-9a-aza-9a-homoerythromycin A or 5-O-desosaminyl-9-deoxo-9-dihydro-9a-aza-9a-homoerithronolide A general formula 2



450

2

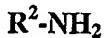
wherein R represents H or cladinosyl group with 4-(chlorosulfonyl)phenyl isocyanate formula 3,



3

455

are subjected to a reaction with ammonia or amine of general formula 4,



4

460

wherein R² represents H or phenyl, 2-pyridyl, 3,4-dimethyl-5-isoxazolyl or 5-methyl-3-isoxazolyl group, in toluene, xylene or some other aprotic solvent, at a temperature 0-110°C and then, if appropriate, to a reaction with inorganic or organic acids.

15. Pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antibacterially effective amount of the substances according to claim 1.

- 465 16. A use of a substance of according to any claims 1-13 for preparing compositions for
sterilization rooms and medical instruments as well as for protection of wall and
wooden coatings.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/HR 03/00058A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H17/08 A61K31/7048

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	KUJUNDZIC, N. ET AL: "Azalides: synthesis and antibacterial activity of novel 9a-(N'-substitute carbamoyl and thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY (1995), 30(6), 455-62 , 1995, XP004040166 the whole document ----	

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the International search

24 February 2004

Date of mailing of the International search report

03/03/2004

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Klein, D

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/HR 03/00058

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